Schering-Plough
Research Institute

2326 '02 JUL -1 A9:47

144 Route 94
P.O. Box 32
Lafayette, New Jersey 07848-0032
Telephone (973) 940-4100

June **26, 2002**

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Ref: Draft Guidance for Reviewers on the Integration of Study Results to Assess Concerns About Human Reproductive and Developmental Toxicities
Docket No. 99N-2079, CDER 2001100

Schering Plough is pleased to have the opportunity to provide comments on the draft Reviewer Guidance "Integration of Study Results to Assess Concerns About Human Reproductive and Developmental Toxicities published in the Federal Register on November 13,2001.

We believe that the updated version of the document is a positive step toward more consistent interpretation of complex reproductive and developmental toxicology data for the benefit of the authors and reviewers of the submitted studies. However, in order to better serve the public who consume the drugs and the physicians who need to counsel patients, we recommend that the end result of the Integrative Assessment Tool (IAT) not be based on arbitrary numerical cutoffs, but on a summary narrative of evaluation that leads to a clear summary risk statement to be used in product labeling. In addition, since this document will be used by many persons with varying understanding of reproductive toxicology data, we would like to request that this document be as complete and clear as possible. Specific suggestions regarding the document follow.

Types of Reproductive and Developmental Toxicity Evaluated
Page 2;Line 76:

We suggest that due to the potential differences between effects on male and/or female fertility that fertility be separated into male fertility and female fertility.

Signals for Related Types of Reproductive and Developmental Toxicity
Page 8;Lines 336-338

Although positive signals for related classes of toxicity are often seen, if adequate studies are conducted we do not believe that the final evaluation need state that there were no effects for a given endpoint, but that positive signals were seen for other "related

99N-2079 C14

toxicities." Reproductive effects can be specific and guilt by association is not often appropriate.

Cross-Species Concordance
Page 10; Lines 430-433

Since some reproductive endpoints are only assessed in one species we suggest that there should be unchanged concern if a study is only conducted in one species to better clarify how to address this probability which occurs in common study paradigms.

Maternal Toxicity
Page 11; Lines 494-496

The ICH guidelines for conduct of reproductive testing necessitate utilization of a dose that causes maternal toxicity when possible. Given this common effect seen in reproductive toxicology testing, this factor is biased toward a +1 score. In addition, the data is not readily available to reasonably attribute most effects seen to maternal toxicity with the possible exceptions of skeletal ossification and rabbit abortion/resorptions. We suggest that concern be unchanged if effects observed only in the presence of frank maternal toxicity and be decreased if they can be attributed to maternal toxicity.

Dose-Response Relationship
Page 11; Lines 514-524

Dose response relationship should be integral in assessing if there is a positive signal and we suggest removing this as a factor and including the idea under determination of a positive signal. If it is to remain as a factor, we suggest that the presence of adverse events at the high dose alone would cause concern to be unchanged. One other caveat in putting much weight in this signal is the dependence of this relationship on appropriate dose selection/spacing.

Rare Events
Page 11; Lines 534-546

We believe that this signal should be removed because it is primarily important in determining if one has a positive signal.

Therapeutic Index
Page 13; Lines 555-588

The numbers stated in this section appear arbitrary (why is > 20 needed for decreased concern?) and should be justified. In addition TD10 and ED90 data is often not available in the same species, malung this ratio even more arbitrary. If this data is available in one species, we suggest use of the LOEL as the numerator and the pharmacologically effective dose as the denominator using the same TK metric to establish a more realistic number. When data are not available no ratio should be determined unless use of a cross-species comparison can be justified.

Similarity between Pharmacologic and Reproductive Developmental Toxicologic Mechanisms
Page 14; Lines 603-612

We believe that concern should be unchanged if it is not known that the positive signal is an extension of the pharmacologic effect of the drug. In cases where the positive signal is attributed to an animal-specific pharmacological response, we believe that this should be important in determination of positive signal rather than just decreased concern.

Metabolic and Drug Distribution Profiles and General Toxicity Profiles
Page 15; Lines 620-640

In these sections, if an appropriate animal model is used (appropriate PK, similar toxicity), these factors bias toward a +1 rating each. We believe that concern should only be increased if it is known that ADME or general toxicity is important in the reproductive effects and unchanged concern if the role of these factors in the effects seen isn't known. Again, if the effects are known to be due to an animal-specific toxicity or metabolite, this should factor into determination of a positive signal rather than a –1 rating.

Kinetic Comparison of Relative Exposure
Page 16; 686-687, 695-700

The numerical cutoffs for the relative exposure ratios appear arbitrary and should be justified-especially in light of the lack of knowledge regarding human fetal exposure to really understand the therapeutic level in humans. In addition, we disagree with having to take relative interspecies differences in protein binding into account since one also doesn't know the relative protein binding in the organism of interest-the human fetus.

Class Alerts
Page 17; Lines 729-742

We believe that the state of the science regarding actual prediction of human risk based on chemical structure is not available. We would prefer that this factor be assessed with respect to compound's similar modes of action, rather than similar structures. In addition, concern should be decreased if it is known that a compound with a similar mode of action is known **not** to cause any reproductive or developmental toxicity in humans and unchanged if it isn't known to cause (or to not cause) human effects.

Summary Risk Conclusions
Page 18; Lines 792-805

As stated previously we recommend that the final product of the IAT be more instructive to the patient and clinician and contain narrative summary statements regarding risk. We advocate only *2* categories-Does not predict an increased risk of (finding) or Does predict an increased risk of (finding(s)) in conjunction with pertinent conditions/caveats for better understanding of the finding(s) in the context of the data. Maintenance of the "may increase risk" category is similar to the nebulous category C labeling that we have at the current time. In addition, we do not agree with having arbitrary numerical cutoffs dictate patient risk. With the suggested numbers, there is a lot

of leeway and how can one justify a –2 and a +2 rating inferring the same risk-and is a +2 really different than a +3?

Sincerely,

Dr. Kimberley Treinen
Director, Reproductive Toxicology and Teratology

4019 (7/00)

Dr. Kimberley Tyrrell
Schering-Plough Research Institute
144 Route 94
P.O. Box 32
Lafayette NJ 07848-0032

LAFAYETTE NJ JUN26'02 PB METER 8212567 ≈ 0.34 U.S.POSTAGE

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

20857+0001